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ATTORNEY DOCKET NO. 10010381-1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Steven Lefkowitz

Serial No.: 09/944,083 **Examiner:** My Chau T Tran

Filing Date: August 31, 2001 **Group Art Unit:** 1639

Title: METHODS FOR GENERATING LIGAND ARRAYS VIA DEPOSITION OF LIGANDS ONTO OLEFIN DISPLAYING SUBSTRATES, AND ARRAYS PRODUCED THEREBY

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF

Sir:

Transmitted herewith is the Appeal Brief in this application with respect to the Notice of Appeal filed on 2-1-2005

The fee for filing this Appeal Brief is (37 CFR 1.17(c)) **$500.00**.

(complete (a) or (b) as applicable)

The proceedings herein are for a patent application and the provisions of 37 CFR 1.136(a) apply.

☒ (a) Applicant petitions for an extension of time under 37 CFR 1.136 (fees: 37 CFR 1.17(a)(1)-(5)) for the total number of months checked below:

☒	one month	$ 120.00
☐	two months	$ 450.00
☐	three months	$1020.00
☐	four months	$1590.00

☐ The extension fee has already been filled in this application.

☐ (b) Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition and fee for extension of time.

Please charge to Deposit Account **50-1078** the sum of $620.00. At any time during the pendency of this application, please charge any fees required or credit any overpayment to Deposit Account **50-1078** pursuant to 37 CFR 1.25.

A duplicate copy of this transmittal letter is enclosed.

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☒ I hereby certify that this correspondence is being deposited with the United States Postal Service as ~~first class~~ mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date of Deposit: 05-02-2005 **OR**

☐ I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.

Date of Facsimile:

Typed Name: Donna Macedo

Signature: Donna Macedo

Respectfully submitted,

Steven Lefkowitz

By

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APPELLANTS' BRIEF Address to: Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Application Number	09/944,083
	Confirmation Number	1180
	Attorney Docket No.	10010381-1
	Filing Date	August 31, 2001
	First Named Inventor	Steven Lefkowitz
	Examiner	My Chau T Tran
	Group Art	1639
	Title: *Methods for Generating Ligand Arrays Via Deposition of Ligands onto Olefin Displaying Substrates, and Arrays Produced Thereby*	

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Rejection dated November 3, 2004. No claims have been allowed, and Claims 7-26 and 44-51 are pending. Claims 7-26 and 44-51 are appealed. A Notice of Appeal was filed on February 1, 2005. In light of the enclosed petition for a 1 month extension of time this Appeal Brief is timely filed.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

The Commissioner is hereby authorized to charge deposit account number 50-1078, reference no. 10010381-1 to cover the fee required under 37 C.F.R. §1.17(c) for filing Appellants' brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-1078, reference no. 10010381-1.

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REAL PARTY IN INTEREST

The inventors named on this patent application assigned their entire rights to the invention to Agilent Technologies, Inc.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

The present application was filed on August 31, 2001 with Claims 1-47. During the course of prosecution, Claims 1-6 and 27-43 were canceled, Claims 48-51 were added and Claims 7 and 16 were amended. Accordingly, Claims 7-26 and 44-51 are pending in the present application, all of which are appealed herein.

STATUS OF AMENDMENTS

No amendments to the Claims were filed subsequent to issuance of the Final Rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention is drawn to methods of producing ligand arrays, e.g., polypeptide and nucleic acid arrays, as well as the arrays produced thereby. In the claimed methods, a substrate having a surface displaying olefinic functional groups, e.g., olefin groups having a single site of unsaturation (α-olefins), are modified such that the olefinic functional groups are converted to ligand reactive functional groups. The resultant substrate is then contacted with, typically, at least two different ligands, e.g., via deposition of each different ligand onto a different region of the surface, resulting in covalent attachment of the contacted ligand to the surface via reaction with the ligand reactive functional groups present on the substrate surface. Ligand arrays produced via the subject methods demonstrate a number of desirable properties, e.g., nucleic acid arrays produced by the subject methods provide high signal intensity with low

background in nucleic acid hybridization assays, etc.

Below is a description of each appealed claim and where support for each can be found in the specification. Each paragraph describing the claims begins with an independent claim and describes all claims dependent thereon.

Independent Claim 7 claims a three-step method of producing an array of at least two different polymer ligands covalently attached to a surface of a substrate. The first step (a) comprises providing a substrate having a surface displaying olefin functional groups that consist of a single site of unsaturation by contacting said surface with a derivatizing composition comprising at least a first silane having an olefin functional group (specification at page 7 lines 6-9, page 8 lines 14-22, page 9 lines 2-3). The second step (b) comprises converting the olefin functional groups to ligand reactive functional groups that produce covalent bonds with the at least two different polymer ligands upon contact with the ligands (specification at page 8 lines 5-7). The third step (c) comprises contacting the surface with the at least two different polymer ligands to covalently bond the at least two different polymer ligands to the surface and produce the array (specification at page 7, lines 9-12). Claim 8 is dependent on Claim 7 and specifies that the polymer ligands are nucleic acids (specification at page 13 line 27). Claim 9 depends from Claim 7 and specifies that the ligands are peptides (specification at page 13 line 27). Claim 10 depends from Claim 7 and specifies that the contacting step (c) comprises depositing each of the at least two different polymer ligands in a different region of the surface (specification at page 7 lines 9-12). Claim 11 depends from Claim 7 and specifies that the ligand reactive functional group produced by the converting step (b) is an aldehyde (specification at page 11 lines 7-9). Claim 12 depends from Claim 11 and specifies that the aldehyde is a benzaldehyde (specification at page 12 lines 5-7). Claim 13 depends from Claim 7 and specifies that the ligand reactive functional group produced by the converting step (b) is an activated carboxylate ester (specification at page 12 lines 15-16). Claim 14 is dependent on Claim 7and specifies that the ligand reactive functional group produced by the converting step (b) is an amine (specification at page 12 lines 23-24). Claim 15 depends from Claim 7 and specifies that the ligand reactive functional group produced by the converting step (b) is an imidazolyl carbamate (specification at page 12 lines 29-31). Claim 44 depends from Claim 7 and additionally comprises reading the array following exposure of the array to

a sample (specification at page 27 lines 16-25, page 18 lines 8-12). Claim 48 depends from Claim 7 and specifies that the olefin functional groups that consist of a single site of unsaturation each comprise a terminal -CH=CH_2 moiety (page 10 lines 4-12). Claim 50 depends from Claim 7 and specifies that the first silane having an olefin functional group is undecenyltrichlorosilane (specification at page 19 lines 18-22).

Independent Claim 16 claims a three-step method of producing an array of at least two different nucleic acids covalently attached to a surface of a substrate. The first step (a) comprises providing a substrate having a surface displaying olefin functional groups that consist of a single site of unsaturation by contacting said surface with a derivatizing composition comprising at least a first silane having an olefin functional group (specification at page 7 lines 6-9, page 8 lines 14-22, page 9 lines 2-3). The second step (b) comprises converting the olefin functional groups to reactive functional groups that produce covalent bonds with the at least two different nucleic acids upon contact with said nucleic acids (specification at page 8 lines 5-7). The third step (c) comprises depositing at least two different nucleic acids onto different regions of said surface to covalently bond said at least two different nucleic acids to the surface and produce said array (specification at page 7 lines 9-12, page 13 lines 30-32). Claim 17 depends from Claim 16 and specifies that the nucleic acids are oligonucleotides (specification at page 13 lines 32-33). Claim 18 depends from Claim 16 and specifies that the nucleic acids are polynucleotides (specification at page 13 lines 32-33). Claim 19 depends from Claim 18 and specifies that the polynucleotides are cDNAs (specification at page 13 lines 32-33). Claim 20 depends from Claim 16 and specifies that the ligand reactive functional group produced by the converting step (b) is an aldehyde (specification at page 11 lines 7-9). Claim 21 depends from Claim 20 and specifies that the aldehyde is a benzaldehyde (specification at page 12 lines 5-7). Claim 22 depends from Claim 16 and specifies that the ligand reactive functional group produced by the converting step (b) is an activated carboxylate ester (specification at page 12 lines 15-16). Claim 23 is dependent on Claim 16 and specifies that the ligand reactive functional group produced by the converting step (b) is an amine (specification at page 12 lines 23-24). Claim 24 depends from Claim 16 and specifies that the ligand reactive functional group produced by the converting step (b) is an imidazolyl carbamate (specification at page 12 lines 29-31). Claim 49 depends from Claim 16 and specifies

that the olefin functional groups that consist of a single site of unsaturation each comprise a terminal -CH=CH_2 moiety (page 10 lines 4-12). Claim 51 depends from Claim 16 and specifies that the first silane having an olefin functional group is undecenyltrichlorosilane (specification at page 19 lines 18-22).

Independent Claim 25 claims a ligand array produced according to the method of Claim 7 (specification at page 7 lines 4-6 and page 16 line 7).

Independent Claim 26 claims a ligand array produced according to the method of Claim 16 (specification at page 7 lines 4-6 and page 16 line 7).

Independent Claim 45 claims a method comprising forwarding data representing a result of a reading obtained by the method of Claim 44 (page 18 lines 17-30). Claim 46 depends from Claim 45 and specifies that the data is transmitted to a remote location (page 18 lines 18-19).

Independent Claim 47 claims a method comprising receiving data representing a result of an interrogation obtained by the method of Claim 44 (specification at page 18 lines 17-30).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 7-26 and 44-51 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wang et al. (US Patent 5,922,617) in view of Bensimon et al. (US Patent 5,846,724).

II. Claims 7-26 and 44-51 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Pirrung et al. (US Patent 5,143,854) in view of Bensimon et al. (US Patent 5,677,126).

ARGUMENT

I. Claims 7-26 and 44-51 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Wang et al. (US Patent 5,922,617) in view of Bensimon et al. (US Patent 5,846,724).

The Appellants wish to group the Claims as follows: Claims 7-10, 16-19, 50 and 51 as a first group; Claims 11, 12, 20 and 21 as a second group; Claims 13 and 22 as a third group; Claims 14 and 23 as a fourth group; and Claims 15 and 24 as a fifth group.

With respect to rejections made under 35 U.S.C. § 103, MPEP § 2142 states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

It is respectfully submitted that the Examiner's *prima facie* case of obviousness is deficient because the combined teachings of the cited prior art fail to render the claimed invention obvious. Below are the contentions of the Appellant with respect to each ground of rejection, with a separate subheading for each group of claims.

Group I: Claims 7-10, 16-19, 50 and 51

The claimed invention of this group is drawn to methods of producing an array of at least two different polymer ligands (as in independent Claims 7), or specifically nucleic acids (as in independent Claim 16), covalently attached to a surface of a substrate. The first step (a) comprises providing a substrate having a surface displaying olefin functional groups that consist of a single site of unsaturation by contacting said surface with a derivatizing composition comprising at least a first silane having an olefin functional group. The second step (b) comprises converting the olefin functional groups to ligand reactive functional groups that produce covalent bonds with the at least two different polymer ligands upon contact with the ligands. The third step (c) comprises contacting the surface with the at least two different polymer ligands to covalently bond the at least two different polymer ligands to the surface and produce the array.

Therefore, an element of the claimed methods is to convert the olefin functional groups to ligand reactive functional groups, prior to contacting the substrate with the ligand to be attached thereto (see Figure 1, below).

In the Final Office Action dated November 3, 2004, the Examiner asserts that Wang et al. disclose methods and devices for rapidly screening a large number of events. The Examiner further asserts that the devices contain a microarray of bound components and that the methods comprise preparing the microarray by modifying the surface of the solid substrate by the introduction of functionalities (e.g., amino groups,

activated halides, carboxyl groups, mercaptan groups, epoxides), which would react with the bound components (e.g., nucleic acids or proteins). The Examiner further asserts that the linkages may be amides, amidines, amines, esters, ethers, thioethers, dithioethers, and the like. The Examiner further asserts that the method of Wang et al. further comprises assaying the microarray by detecting the signal produced using a disk scanner.

The Examiner acknowledges that Wang et al. does not teach the method step of contacting the surface with a derivatizing composition comprising at least a first silane having an olefin functional group to produce a substrate having a surface displaying olefin functional groups.

To remedy this deficiency, the Examiner cites Bensimon et al., asserting that this reference discloses a method of making highly specific surfaces for biological reactions, because the method of Bensimon comprises functionalizing a support with a variety of silane derivatives that would result in a surface group with a double bond on the substrate and directly anchoring the molecules of biological interest (e.g., DNA, RNA, PNA, proteins, lipids and saccharides).

In making this rejection, the Examiner cites two passages from Bensimon et al. which read as follows:

> They [surface groups with double bond, or C=C] are capable of directly anchoring molecules of biological interest (DNA, RNA, PNA, proteins, lipids, saccharides) under certain conditions of pH or ionic content of the medium. (*col. 3 lines43-46*)
>
> Within the framework of the present invention, it has been demonstrated that these surfaces have a reactivity which is highly pH-dependent. This characteristic makes it possible to anchor the nucleic acids or the proteins, especially by their end(s), using a determined pH region and often with a reaction rate which can be controlled by the pH. (*col. 6 lines 50-56*)

The Examiner has interpreted these passages as teaching a "converting step," maintaining that controlling the reactivity of the C=C surface by pH or ionic content of the medium is itself a converting step. As stated on page 4 in the second full paragraph of the Advisory Action dated February 28, 2005:

> Third, Bensimon et al. do teach the presently claimed converting step. Bensimon et al. discloses the step of controlling the reactivity of the C=C surface by pH or ionic contents, i.e. *"converting said olefin functional groups to ligand reactive functional groups"*, to directly anchor the biological interest such as DNA, i.e. to *"produce covalent bonds"* (see col. 4, lines 15- 18, and col. 7, lines 26-32). Thus, Bensimon et al. do teach the presently claimed converting step.

However, the Appellants submit that these sections of Bensimon et al. provide no teaching of converting olefin functional groups to ligand reactive functional groups as is claimed in the subject application. Bensimon et al. fail to disclose that the olefin functional group is converted to a distinct ligand reactive functional group under their reaction conditions (specific pH range). Rather, Bensimon et al. make clear that the effect of pH is to enhance the reactivity of the C=C group (or radical) and not to convert it to a distinct ligand reactive moiety (col. 6, lines 47-56):

> With an exposed group containing a $-CH=CH_2$ radical which will be called hereinafter "C=C surface" or "surface with ethylenic bond", a direct anchoring, in particular of DNA or proteins is possible. Within the framework of the present invention, it has been demonstrated that these surfaces have a reactivity which is highly pH-dependent. This characteristic makes it possible to anchor the nucleic acids or the proteins, especially by their end(s), using a determined pH region and often with a reaction rate which can be controlled by the pH.

Furthermore, the Appellants submit that Bensimon et al. specifically exclude a converting step as is claimed in the subject application. For support of this position, the Appellants point to col. 3 lines 40-50 of Bensimon et al. which states:

> These highly specific surfaces for biological reactions, contain a support having at the surface groups with a double bond, especially vinyl (-CH=CH2, hereinafter C=C surfaces) which are accessible to the solution. They are capable of **directly anchoring molecules of biological interest** (DNA, RNA, PNA, proteins, lipids, saccharides) under certain conditions of pH or ionic content of the medium. In particular, **these surfaces do not require specific chemical modifcation either of the surface or of the biological molecules to be anchored**. There are no documents mentioning such a use of a surface with vinyl groups. (*emphasis added*)

Accordingly, Bensimon et al. specifically discloses a method in which the olefin functional groups on the surface are reacted directly with the ligands to be attached to the surface without any intermediate conversion step (see Figure 1A, below). Because this direct linkage ability without an intermediate conversion step is stated as a benefit of using the disclosed method, Bensimon et al. provides no motivation to one of skill in the art to include an additional step of first changing the olefin group to a distinct ligand reactive moiety. In other words, Bensimon et al. specifically teach away from an olefin group-converting step.

With regard to establishing a *bona fide prima facie* case of obviousness, the MPEP states in § 2141.02:

> A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)

As such, the Appellants submit that Bensimon fails to teach or suggest the step of converting the olefin functional group to a ligand reactive functional group and in fact teaches away from such a step.

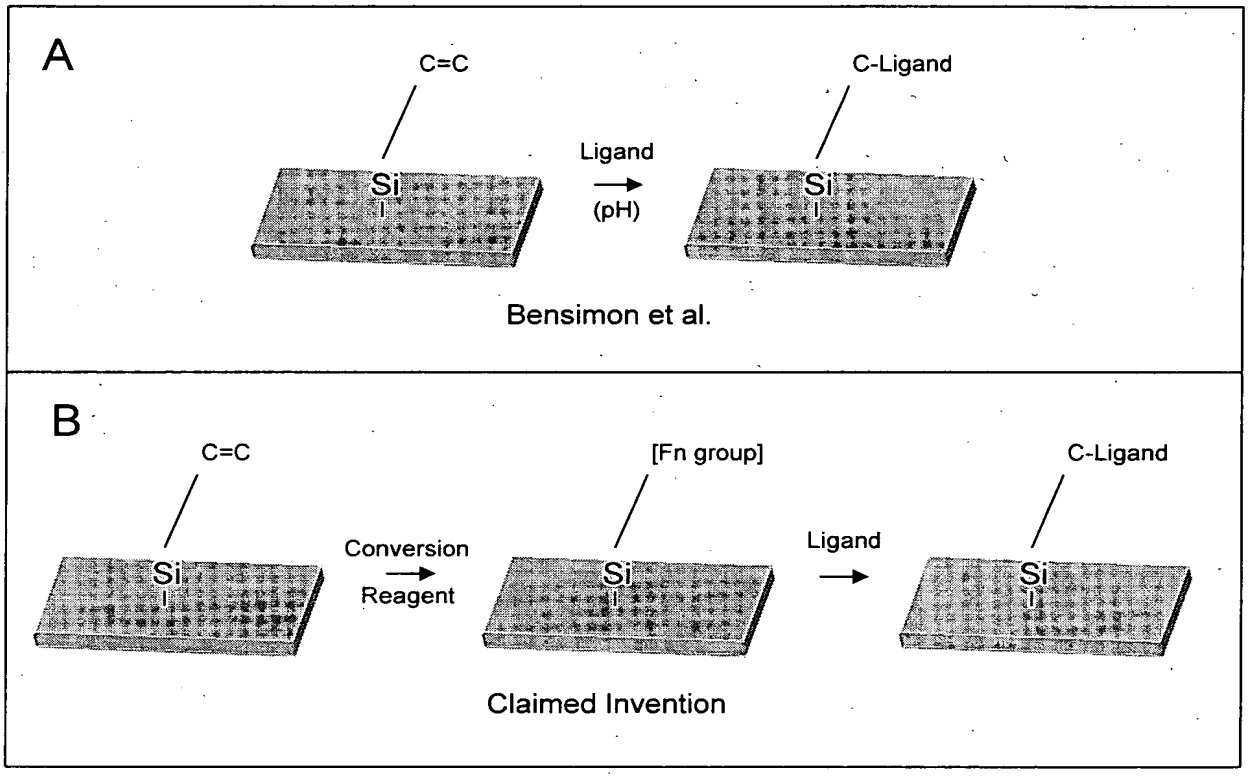

Figure 1. Comparison of teachings of (A) Bensimon et al. with (B) the claimed invention. As argued in this Appeal Brief, none of the cited references to teach or suggest the step of converting the olefin functional group (C=C) to a distinct ligand reactive functional group [Fn group] prior to contacting the substrate with the ligand.

As such, combining the teaching of Wang with Bensimon actually teaches away from the claimed invention, which requires the presence of the olefin converting step prior to the ligand attachment step.

On page 4 lines 5-14 of the Advisory Action dated February 28, 2005, the Examiner states:

> ....., the presently claimed step of *"converting said olefin functional groups to ligand reactive functional groups that produce covalent bonds with said at least two different polymer ligands upon contact with said ligands"* of claim 7 does not

> impart any structural characteristic of an "intermediate" moiety but rather a functional characteristic of the claimed olefin functional group, i.e. a *"ligand reactive functional groups that produce covalent bonds with"* the ligand. Thus, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., an "intermediate" moiety) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns,* 988 F.2d 1181,26 USPQ2d 1057 (Fed. Cir. 1993).

However, as reviewed above, the claims require that the olefin functional group be converted to a distinct (or "intermediate") moiety. This step is elaborated in the specification on page 10, line 33 to page 11, line 13:

> By ligand reactive functional groups is meant groups that react with moieties present on the target ligands, (i.e., the ligands to be deposited onto the surface and covalently bound thereto) in manner that produces a covalent bond or linkage between the ligand and the substrate surface. **The olefinic functional groups may be converted to a variety of different types of reactive moieties** using a variety of different protocols, depending on the particular nature of the ligand that is to be covalently bound to the substrate surface. Representative ligand reactive functional groups to which the initial olefinic functional groups may be converted include: alcohols, aldehyes, activated carboxylates, amines, imidazolyl carbamates, mercaptans, anhydrides, and the like. The particular ligand reactive functional group to which the initial olefinic group is converted will be chosen, at least in part, on considerations that include, but are not limited to: the nature of the ligand and functional groups that may be present thereon, ease of conversion, and the like: (*emphasis added*)

As such, the claimed converting step is a positive method step that changes the nature of the olefin group to a ligand reactive function group. Therefore, the Examiner's assertion that "features upon which applicant relies (i.e., an "intermediate" moiety) are not recited in the rejected claim(s)" is without merit, and the conversion step cannot be discounted as not imparting any patentable distinction to the claimed methods.

In summary, the Appellants submit that Wang et al. in view of Bensimon et al. fail to teach or suggest each and every element of the claimed invention. Specifically these cited references fail to teach the step of converting olefin functional groups to ligand reactive functional groups that produce covalent bonds with ligands upon contact. Indeed, the Appellants submit that Bensimon et al. teach away from such an element.

As such, the Appellants respectfully request withdrawal of the rejection of Claims 7-10, 16-19, 50 and 51 as being unpatentable under 35 U.S.C. § 103(a) over Wang et al. in view of Bensimon et al.

Group II: Claims 11, 12, 20 and 21

The claims of this group specify that the ligand reactive functional group produced by the converting step (b) of the claimed methods is an aldehyde (Claims 11 and 20) or, more specifically, a benzaldehyde (Claims 12 and 21).

In addition to the arguments detailed above for the Claims of Group I, the Appellants further submit that neither Wang et al. nor Bensimon et al. teach or suggest the conversion of an olefin functional group to any aldehyde, much less a benzaldehyde, ligand reactive functional group.

As such, because the combination of the teachings of Wang et al. and Bensimon et al. fail to teach of suggest each and every element of these claims, the Appellants respectfully request withdrawal of this rejection.

Group III: Claims 13 and 22

The claims of this group specify that the ligand reactive functional group produced by the converting step (b) of the claimed methods is an activated carboxylate ester.

In addition to the arguments detailed above for the Claims of Group I, the Appellants further submit that neither Wang et al. nor Bensimon et al. teach or suggest the conversion of an olefin functional group to an activated carboxylate ester ligand reactive functional group.

As such, because the combination of the teachings of Wang et al. and Bensimon et al. fail to teach of suggest each and every element of these claims, the Appellants respectfully request withdrawal of this rejection.

Group IV: Claims 14 and 23

The claims of this group specify that the ligand reactive functional group produced by the converting step (b) of the claimed methods is an amine.

In addition to the arguments detailed above for the Claims of Group I, the Appellants further submit that neither Wang et al. nor Bensimon et al. teach or suggest the conversion of an olefin functional group to an amine ligand reactive functional group.

As such, because the combination of the teachings of Wang et al. and Bensimon et al. fail to teach of suggest each and every element of these claims, the Appellants respectfully request withdrawal of this rejection.

Group V: Claims 15 and 24

The claims of this group specify that the ligand reactive functional group produced by the converting step (b) of the claimed methods is an imidazolyl carbamate.

In addition to the arguments detailed above for the Claims of Group I, the Appellants further submit that neither Wang et al. nor Bensimon et al. teach or suggest the conversion of an olefin functional group to an imidazolyl carbamate ligand reactive functional group.

As such, because the combination of the teachings of Wang et al. and Bensimon et al. fail to teach of suggest each and every element of these claims, the Appellants respectfully request withdrawal of this rejection.

II. Claims 7-26 and 44-51 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Pirrung et al. (US Patent 5,143,854) in view of Bensimon et al. (US Patent 5,846,724).

The Appellants wish to group the Claims as follows: Claims 7-10, 16-19, 50 and 51 as a first group; Claims 11, 12, 20 and 21 as a second group; Claims 13 and 22 as a third group; Claims 14 and 23 as a fourth group; and Claims 15 and 24 as a fifth group.

With respect to rejections made under 35 U.S.C. § 103, MPEP § 2142 states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

It is respectfully submitted that the Examiner's *prima facie* case of obvious is deficient because the combined teachings of the cited prior art fail to render the claimed invention obvious. Below are the contentions of the Appellant with respect to each ground of rejection, with a separate subheading for each group of claims.

Group I: Claims 7-10, 16-19, 50 and 51

The claimed invention of this group is drawn to methods of producing an array of at least two different polymer ligands (as in independent Claims 7), or specifically nucleic acids (as in independent Claim 16), covalently attached to a surface of a substrate. The first step (a) is providing a substrate having a surface displaying olefin functional groups that consist of a single site of unsaturation by contacting said surface with a derivatizing composition comprising at least a first silane having an olefin functional group. The second step (b) is converting the olefin functional groups to ligand reactive functional groups that produce covalent bonds with the at least two different polymer ligands upon contact with the ligands. The third step (c) is contacting the surface with the at least two different polymer ligands to covalently bond the at least two different polymer ligands to the surface and produce the array.

Therefore, an element of the claimed methods is to convert the olefin functional groups to ligand reactive functional groups, a step that is neither taught nor suggested in the cited references (see Figure 1 in the previous section).

Similar to the above rejection based on Wang in combination with Bensimon, the Examiner asserts that Pirrung et al. discloses all of the elements of the claimed method but for the method step of contacting the surface with a derivatizing composition comprising at least a first silane having an olefin functional group to produce a substrate having a surface displaying olefin functional groups.

To remedy this deficiency, the Examiner cites Bensimon et al., asserting that this reference discloses functionalizing a support with a variety of silane derivatives that would result in a surface group with a double bond on the substrate and directly anchoring the molecules of biological interest (e.g., DNA, RNA, PNA, proteins, lipids and saccharides).

In making this rejection, the Examiner cites two passages from Bensimon et al. which read as follows:

> They [surface groups with double bond, or C=C] are capable of directly anchoring molecules of biological interest (DNA, RNA, PNA, proteins, lipids, saccharides) under certain conditions of pH or ionic content of the medium. (*col. 4 lines15-18*)
>
> Within the framework of the present invention, it has been demonstrated that these surfaces have a reactivity which is highly pH-dependent. This

> characteristic makes it possible to anchor the nucleic acids or the proteins, especially by their end(s), using a determined pH region and often with a reaction rate which can be controlled by the pH. (*col. 7 lines 26-32*)

The Examiner has interpreted these passages as teaching a "converting step" maintaining that controlling the reactivity of the C=C surface by pH or ionic content of the medium is itself a converting step. As stated on page 4, in the second full paragraph of the Advisory Action dated February 28, 2005:

> Third, Bensimon et al. do teach the presently claimed converting step. Bensimon et al. discloses the step of controlling the reactivity of the C=C surface by pH or ionic contents, i.e. *"converting said olefin functional groups to ligand reactive functional groups"*, to directly anchor the biological interest such as DNA, i.e. to *"produce covalent bonds"* (see col. 4, lines 15- 18, and col. 7, lines 26-32). Thus, Bensimon et al. do teach the presently claimed converting step.

However, the Appellants submit that these sections of Bensimon et al. provide no teaching of converting olefin functional groups to ligand reactive functional groups as is claimed in the subject application. Bensimon et al. fail to disclose that the olefin functional group is converted to a distinct ligand reactive functional group under their reaction conditions (specific pH range). Rather, Bensimon et al. make clear that the effect of pH is to enhance the reactivity of the C=C group (or radical) and not to convert it to a distinct ligand reactive moiety (col. 7, lines 23-32):

> With an exposed group containing a $-CH=CH_2$ radical which will be called hereinafter "C=C surface" or "surface with ethylenic bond", a direct anchoring, in particular of DNA or proteins is possible. Within the framework of the present invention, it has been demonstrated that these surfaces have a reactivity which is highly pH-dependent. This characteristic makes it possible to anchor the nucleic acids or the proteins, especially by their end(s), using a determined pH region and often with a reaction rate which can be controlled by the pH.

Furthermore, the Appellants submit that Bensimon et al. specifically exclude a converting step as is claimed in the subject application. For support of this position, the Appellants point to col. 3 lines 40-50 of Bensimon et al. which states:

> These highly specific surfaces for biological reactions, contain a support having at the surface groups with a double bond, especially vinyl (-CH=CH2, hereinajler C=C surfaces) which are accessible to the solution. They are capable of **directly anchoring molecules of biological interest** (DNA, RNA, PNA, proteins, lipids, saccharides) under certain conditions of pH or ionic content of the medium. In particular, **these surfaces do not require specific chemical modifcation either of the surface or of the biological molecules to be anchored**. There are no documents mentioning such a use of a surface with vinyl groups. (*emphasis added*)

Accordingly, Bensimon et al. specifically discloses a method in which the olefin functional groups on the surface are reacted directly with the ligands to be attached to the surface without any intermediate conversion step (see Figure 1A in the previous section). Because this direct linkage ability without an intermediate conversion step is stated as a benefit of using the disclosed method, Bensimon et al. provides no motivation to one of skill in the art to include an additional step of first changing the olefin group to a distinct ligand reactive moiety. In other words, Bensimon et al. specifically teach away from an olefin group converting step.

With regard to establishing a *bona fide prima facie* case of obviousness, the MPEP states in § 2141.02:

> A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)

As such, the Appellants submit that Bensimon fails to teach or suggest the step of converting the olefin functional group to a ligand reactive functional group and in fact teaches away from such a step.

On page 4 lines 5-14 of the Advisory Action dated February 28, 2005, the Examiner states:

> ....., the presently claimed step of *"converting said olefin functional groups to ligand reactive functional groups that produce covalent bonds with said at least two different polymer ligands upon contact with said ligands"* of claim 7 does not impart any structural characteristic of an "intermediate" moiety but rather a functional characteristic of the claimed olefin functional group, i.e. a *"ligand reactive functional groups that produce covalent bonds with"* the ligand. Thus, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., an "intermediate" moiety) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In **re** Van Geuns*, 988 F.2d 1181,26 USPQ2d 1057 (Fed. Cir. 1993).

However, as reviewed above, the claims require that the olefin functional group be converted to a distinct (or "intermediate") moiety. This step is elaborated in the specification on page 10 line 33 to page 11 line 13:

> By ligand reactive functional groups is meant groups that react with moieties present on the target ligands, (i.e., the ligands to be deposited onto the surface and covalently bound thereto) in manner that produces a covalent bond or linkage between the ligand and the substrate surface. **The olefinic functional groups may be converted to a variety of different types of reactive**

> **moieties** using a variety of different protocols, depending on the particular nature of the ligand that is to be covalently bound to the substrate surface. Representative ligand reactive functional groups to which the initial olefinic functional groups may be converted include: alcohols, aldehyes, activated carboxylates, amines, imidazolyl carbamates, mercaptans, anhydrides, and the like. The particular ligand reactive functional group to which the initial olefinic group is converted will be chosen, at least in part, on considerations that include, but are not limited to: the nature of the ligand and functional groups that may be present thereon, ease of conversion, and the like. (*emphasis added*)

As such, the claimed converting step is a positive method step that changes the nature of the olefin group to a ligand reactive function group. Therefore, the Examiner's assertion that "features upon which applicant relies (i.e., an "intermediate" moiety) are not recited in the rejected claim(s)" is without merit, and the conversion step cannot be discounted as not imparting any patentable distinction to the claimed methods.

In summary, the Appellants submit that Pirrung et al. in view of Bensimon et al. fail to teach or suggest each and every element of the claimed invention. Specifically these cited references fail to teach the step of converting olefin functional groups to ligand reactive functional groups that produce covalent bonds with ligands upon contact. Indeed, the Appellants submit that Bensimon et al. teach away from such an element.

As such, the Appellants respectfully request withdrawal of the rejection of Claims 7-10, 16-19, 50 and 51 as being unpatentable under 35 U.S.C. § 103(a) over Pirrung et al. in view of Bensimon et al.

Group II: Claims 11, 12, 20 and 21

The claims of this group specify that the ligand reactive functional group produced by the converting step (b) of the claimed methods is an aldehyde (Claims 11 and 20) or, more specifically, a benzaldehyde (Claims 12 and 21).

In addition to the arguments detailed above for the Claims of Group I, the Appellants further submit that neither Pirrung et al. nor Bensimon et al. teach or suggest the conversion of an olefin functional group to any aldehyde, much less a benzaldehyde, ligand reactive functional group.

As such, because the combination of the teachings of Pirrung et al. and Bensimon et al. fail to teach of suggest each and every element of these claims, the Appellants respectfully request withdrawal of this rejection.

Group III: Claims 13 and 22

The claims of this group specify that the ligand reactive functional group produced by the converting step (b) of the claimed methods is an activated carboxylate ester.

In addition to the arguments detailed above for the Claims of Group I, the Appellants further submit that neither Pirrung et al. nor Bensimon et al. teach or suggest the conversion of an olefin functional group to an activated carboxylate ester ligand reactive functional group.

As such, because the combination of the teachings of Pirrung et al. and Bensimon et al. fail to teach of suggest each and every element of these claims, the Appellants respectfully request withdrawal of this rejection.

Group IV: Claims 14 and 23

The claims of this group specify that the ligand reactive functional group produced by the converting step (b) of the claimed methods is an amine.

In addition to the arguments detailed above for the Claims of Group I, the Appellants further submit that neither Pirrung et al. nor Bensimon et al. teach or suggest the conversion of an olefin functional group to an amine ligand reactive functional group.

As such, because the combination of the teachings of Pirrung et al. and Bensimon et al. fail to teach of suggest each and every element of these claims, the Appellants respectfully request withdrawal of this rejection.

Group V: Claims 15 and 24

The claims of this group specify that the ligand reactive functional group produced by the converting step (b) of the claimed methods is an imidazolyl carbamate.

In addition to the arguments detailed above for the Claims of Group I, the Appellants further submit that neither Pirrung et al. nor Bensimon et al. teach or suggest the conversion of an olefin functional group to an imidazolyl carbamate ligand reactive functional group.

As such, because the combination of the teachings of Pirrung et al. and Bensimon et al. fail to teach of suggest each and every element of these claims, the Appellants respectfully request withdrawal of this rejection.

SUMMARY

I. Claims 7-26 and 44-51 are not made obvious under 35 U.S.C. § 103(a) over Wang et al. (US Patent 5,922,617) in view of Bensimon et al. (US Patent 5,846,724) because the cited references fail to teach or suggest the step of converting olefin functional groups to ligand reactive functional groups that produce covalent bonds with ligands upon contact. In addition, the Claims of Groups II to V are drawn to converting the olefin functional group to aldehyde (or benzaldehyde), carboxylate ester, amine or imidazolyl carbamate ligand reactive functional groups, respectively, none of which are taught or suggested in the cited references.

II. Claims 7-26 and 44-51 are not made obvious under 35 U.S.C. § 103(a) over Pirrung et al. (US Patent 5,143,854) in view of Bensimon et al. (US Patent 5,846,724) because the cited references fail to teach or suggest the step of converting olefin functional groups to ligand reactive functional groups that produce covalent bonds with ligands upon contact. In addition, the Claims of Groups II to V are drawn to converting the olefin functional group to aldehyde (or benzaldehyde), carboxylate ester, amine or imidazolyl carbamate ligand reactive functional groups, respectively, none of which are taught or suggested in the cited references.

RELIEF REQUESTED

The Appellants respectfully request that the rejections of Claims 7-26 and 44-51 under 35 U.S.C. §103(a) be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: 5.2.05

By: _____
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CLAIMS APPENDIX

7. A method of producing an array of at least two different polymer ligands covalently attached to a surface of a substrate, said method comprising:

(a) providing a substrate having a surface displaying olefin functional groups that consist of a single site of unsaturation by contacting said surface with a derivatizing composition comprising at least a first silane having an olefin functional group;

(b) converting said olefin functional groups to ligand reactive functional groups that produce covalent bonds with said at least two different polymer ligands upon contact with said ligands; and

(c) contacting said surface with said at least two different polymer ligands to covalently bond said at least two different polymer ligands to said surface and produce said array.

8. The method according to Claim 7, wherein said polymer ligands are nucleic acids.

9. The method according to Claim 7, wherein said polymer ligands are peptides.

10. The method according to Claim 7, wherein said contacting step (c) comprises depositing each of said at least two different polymer ligands in a different region of said surface.

11. The method according to Claim 7, wherein said ligand reactive functional group produced by said converting step (b) is an aldehyde.

12. The method according to Claim 11, wherein said aldehyde is a benzaldehyde.

13. The method according to Claim 7, wherein said ligand reactive functional group produced by said converting step (b) is an activated carboxylate ester.

14. The method according to Claim 7, wherein said ligand reactive functional group produced by said converting step (b) is an amine.

15. The method according to Claim 7, wherein said ligand reactive functional group produced by said converting step (b) is an imidazolyl carbamate.

16. A method of producing an array of at least two different nucleic acids covalently attached to a surface of a substrate, said method comprising:

(a) providing a substrate having a surface displaying olefin functional groups that consist of a single site of unsaturation by contacting said surface with a derivatizing composition comprising at least a first silane having an olefin functional group;

(b) converting said olefin functional groups to reactive functional groups that produce covalent bonds with said at least two different nucleic acids upon contact with said nucleic acids; and

(c) depositing at least two different nucleic acids onto different regions of said surface to covalently bond said at least two different nucleic acids to said surface and produce said array.

17. The method according to Claim 16, wherein said nucleic acids are oligonucleotides.

18. The method according to Claim 16, wherein said nucleic acids are polynucleotides.

19. The method according to Claim 18, wherein said polynucleotides are cDNAs.

20. The method according to Claim 16, wherein said ligand reactive functional group produced by said converting step (b) is an aldehyde.

21. The method according to Claim 20, wherein said aldehyde is a benzaldehyde.

22. The method according to Claim 16, wherein said ligand reactive functional group

produced by said converting step (b) is an activated carboxylate ester.

23. The method according to Claim 16, wherein said ligand reactive functional group produced by said converting step (b) is an amine.

24. The method according to Claim 16, wherein said ligand reactive functional group produced by said converting step (b) is an imidazolyl carbamate.

25. A ligand array produced according to the method of Claim 7.

26. A nucleic acid array produced according to the method of Claim 16.

44. A method according to claim 7 additionally comprising, following exposure of the array to a sample:

reading the array.

45. A method comprising forwarding data representing a result of a reading obtained by the method of Claim 44.

46. A method according to Claim 45 wherein the data is transmitted to a remote location.

47. A method comprising receiving data representing a result of an interrogation obtained by the method of Claim 44.

48. The method according to Claim 7, wherein said olefin functional groups that consist of a single site of unsaturation each comprise a terminal $-CH=CH_2$ moiety.

49. The method according to Claim 16, wherein said olefin functional groups that consist of a single site of unsaturation each comprise a terminal $-CH=CH_2$ moiety.

50. The method according to Claim 7, wherein said first silane having an olefin functional group is undecenyltrichlorosilane.

51. The method according to Claim 16, wherein said first silane having an olefin functional group is undecenyltrichlorosilane.

EVIDENCE APPENDIX

No evidence that qualifies under this heading has been submitted during the prosecution of this application, and as such it is left blank.

RELATED PROCEEDINGS APPENDIX

As stated in the *Related Appeals and Interferences* section above, there are no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal. As such this section is left blank.